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# **Shared genetic influences among childhood shyness, social competences, and cortical responses to emotions**

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**Abstract:**

Visual event-related potentials (ERPs) evoked by facial expressions are useful to map socio-emotional responses among shy children, and to predict transition into social phobia. We investigated the sources of covariation among childhood shyness, social competences, and ERPs to other children's happy, neutral and angry expressions.

Electrophysiological and twin analyses examined the phenotypic and etiological association between an index of childhood shyness, an index of social competences, and ERP responses to facial expressions in 200 twins (mean age: 9.23 years). Multivariate twin analyses showed that the covariation among shyness, social competences, and a composite of a frontal late negative component occurring around 200-400 milliseconds in response to happy, neutral and angry expressions could be entirely explained by shared genetic factors.

A coherent causal structure links childhood shyness, social competences, and the cortical responses to facial emotions. A common genetic substrate can explain the interrelatedness of individual differences for childhood shyness, social competences, and some associated electrophysiological responses to socio-emotional signals.

**Key words:** shyness, social competences, expressions of emotions, twins, event-related potentials (ERP).

## Introduction

A major purpose of translational developmental neuroscience is to understand the transactional processes at the basis of socio-emotional functioning in both healthy and disordered populations (Wiggins & Monk, 2013). However, establishing clear and reciprocally coherent connections between the etiological, the neurofunctional, and the behavioural level remains a daunting task for developmental psychopathologists (Battaglia et al., 2009; Battaglia, 2012; Rutter & Pickles, 2015). The encoding and identification of facial expressions of emotions (EoE) is a popular tool to investigate socio-emotional processes in healthy and clinical populations. The ability to identify and utilize EoE as elements of social communication matures early in life, informs social exchanges in humans and primates, and is influenced by both genetic (Wilmer et al., 2010) and environmental (Moulson, Westerlund, Fox, Zeanah, & Nelson, 2009) factors. The processing of emotional stimuli is a complex function involving multiple cortical and subcortical regions (Vuilleumier & Pourtois, 2007), including areas in the ventral temporal lobe such as the fusiform gyrus and the amygdala (Holmes, Lit, Murphy, Gold, & Crawley, 2003; Ishai, Ungerleider, Martin, Schouten, & Haxby, 1999; Monk, 2008; Stein & Stein, 2008).

Reactivity to EoE has been employed to study socio-emotional responses in children with different degrees of social anxiety and their possible transition into clinical conditions such as social anxiety disorder (SAD; (Battaglia et al., 2012; Jarcho et al., 2013; Lau et al., 2012; Schwartz, Wright, Shin, Kagan, & Rauch, 2003)). While the constructs of childhood social anxiety, withdrawal, and shyness collectively map individual gradients of uneasiness in social contexts, SAD represents a proper clinical condition, with a peak of onset in adolescence (Cartwright-Hatton, McNicol, & Doubleday, 2006; Kessler, Chiu, Demler, Merikangas, & Walters, 2005). These constructs have been employed by different research traditions of developmental psychopathology and developmental science (Gazelle & Rubin, 2010; Rubin, Coplan, & Bowker, 2009). Gazelle & Rubin (2010) compared a model focusing on the concept of behavioural inhibition (BI) and an approach based on shy

temperament in relation to the affective-behavioural profiles of anxious-withdrawn children and their parents and of clinical SAD, and concluded that multilevel interaction models may help solve apparent inconsistencies and promote the integration of different constructs and approaches (Gazelle & Rubin, 2010). Among these diverse but related constructs, the temperamental approach to shyness has three attractive features. First, shyness can be defined in a relatively straightforward, reliable, operational manner as a set of behaviours that indicate discomfort in social interactions and avoidance of novel and uncertain situations (e.g., (Kagan, Reznick, & Snidman, 1988)). Second, it has received validation from biological investigations (e.g., (Schwartz et al., 2003)). Third, longitudinal studies show that it bears a developmental relationship with SAD (Biederman et al., 2001; Hirshfeld-Becker et al., 2007). For example, a retrospective analysis of the US National Comorbidity Survey controlling for neuroticism, self-criticism and perceptions of low maternal care, showed that childhood shyness was specifically associated with lifetime SAD (Cox, MacPherson, & Enns, 2005). Longitudinal general population data further show that shyness at age 10-11 predicts SAD in young adulthood (Mason et al., 2004). Thus, although childhood shyness is not a pathological condition per se, and many children outgrow their shyness into good adaptation (Schwartz et al., 2003), there is an association between childhood shyness and later development of SAD.

From a cognitive perspective, SAD is characterised by information processing biases and higher sensitivity to social cues, including EoEs (Clark & McManus, 2002). Research (e.g., (Tillfors et al., 2001) for a review) on perceptually-induced anxiety has shown altered patterns of cortical activation in patients with diverse anxiety disorders compared with control subjects. Abnormal responses have been reported in cortical areas involved in the emotional evaluative (e.g., visuospatial) processes, namely, the secondary visual, parietal, and temporal, in addition to the prefrontal and orbitofrontal, cortices. Affective stimuli of interpersonal hostility, i.e., angry/ contemptuous EoE, have been found to elicit relatively specific neural responses, such as exaggerated amygdala activation, altered

cerebral visual event-related potentials (ERPs) and altered indexes of visual attention in adults (Birbaumer et al., 1998; Horley, Williams, Gonsalvez, & Gordon, 2003; Stein, Goldin, Sareen, Zorrilla, & Brown, 2002) and children with high indexes of shyness and social anxiety (Battaglia et al., 2004; Battaglia et al., 2012).

Given the role of social stimuli processing in full-blown SAD, the investigation of EoE decoding in shy children may help establish a biological basis between these constructs, and predict the possible transition into later SAD. Previous studies of emotional recognition have shown that shy children have lower accuracy in identifying EoEs (Battaglia et al., 2004; Simonian, Beidel, Turner, Berkes, & Long, 2001; Stirling, Eley, & Clark, 2006) and need greater quantity of information to correctly categorise expressions (Battaglia et al., 2010). Yet, level differences in face identification and as a function of temperament or shyness may be small, especially in older children (Reeb-Sutherland et al., 2015). The investigation of neurophysiological processes underlying behavioural performance with event-related potentials (ERPs) can provide a direct measure of overt and covert brain activity (Banaschewski & Brandeis, 2007; Loo, Lenartowicz, & Makeig, 2015). Because of their excellent temporal resolution, ERPs can be extremely helpful in examining the fast-changing sensory and cognitive functions involved in the processing of emotional stimuli (Thai, Taber-Thomas, & Pérez-Edgar, 2016). Early ERPs map processes of face encoding that are more related to attention biases (Thai et al., 2016), and the physical properties of an external eliciting event (e.g., the presentation of a regular vs. an upside-down inverted human face). Late components (occurring around 300 milliseconds after stimulus onset) are believed to reflect information processing determined by the subject's interplays with the event (Posamentier & Abdi, 2003; Schupp et al., 2000; Schweinberger & Burton, 2003), including individuals' reactivity to the emotional valence of stimuli, such as angry or happy EoE, with facial recognition paradigms.

With their ability monitor part of the neuro-behavioural encoding of emotions, visual ERPs evoked by EoE constitute a valuable research tool to investigate how individual differences in information

processing of socio-emotional stimuli are implicated in childhood shyness and SAD. Shy and socially anxious children may be characterised on the basis of both early (Jetha, Zheng, Schmidt, & Segalowitz, 2012) and late (Battaglia et al., 2005) ERPs evoked by EoE. Early ERPs (such as N170 and P200 components) have been found enhanced during emotional attention shifting, emotion recognition and passive viewing paradigms in individuals with high levels of anxiety (Bar-Haim, Lamy, & Glickman, 2005; Mercado, Carretié, Hinojosa, & Penacoba, 2009; Wieser, Pauli, Reicherts, & Muhlberger, 2010), including social anxiety (Kolassa & Miltner, 2006), suggesting enhanced perceptual processing and early attentional resources towards facial expressions. Some other studies, however, did not find these associations (Jetha et al., 2012; Kolassa et al., 2009; Muhlberger et al., 2009). Abnormal N200/N300 components during emotional go/no-go tasks, reflecting impaired processing of emotional stimuli, have been reported among fearful children (Hum, Manassis, & Lewis, 2013; Lewis, Todd, & Honsberger, 2007) and highly-anxious adults (Rossignol, Philippot, Douilliez, Crommelinck, & Campanella, 2005). Differential associations between ERPs to specific EoE, especially negative emotions such as anger, and shyness/SAD have also been reported (Battaglia et al., 2005; Jetha et al., 2012; Kolassa et al., 2009). In a sample of 9 year-old children, a late posterior negative component occurring around 400 ms after stimulus presentation was associated with shyness in response to passive viewing of neutral and angry faces (Battaglia et al., 2005). The same ERP component, thought to reflect processing/detection of the emotional valence of facial stimuli (Battaglia et al., 2005; Williams et al., 2004), longitudinally predicted the development of DSM-IV SAD (Battaglia et al., 2012), and was associated with greater ventral-limbic white matter anisotropy at age 15 (Taddei, Tettamanti, Zanoni, Cappa, & Battaglia, 2012), which signifies suboptimal white matter integrity and suggests an anatomo-functional basis for suboptimal processing of socio-emotional stimuli. Other studies, however, have found altered cortical activation during the processing of facial stimuli, regardless of the emotional content of the stimuli (Hum et al., 2013; Muhlberger et al., 2009), which may suggest a more general impairment in brain activity during the processing of facial cues in anxiety conditions. Biased discrimination of socially-relevant

information associated with abnormal cortical responses to socio-emotional stimuli may hamper social interactions, reinforce a child's disposition to shyness, and constitute a mechanistic connection between the brain responses to EoE and the development of SAD.

While previous investigations in this field have mostly focused on different dimensions of shyness or SAD, social-interpersonal skills and social competences are additional important mediators of human interpersonal relations from childhood onwards (Ordonana et al., 2013). Social competences can be conceptualised as the harmonious application of effective social conducts, along with the related cognitive and emotion-regulatory abilities, that consent the achievement of constructive peer relationships across different social contexts (Dodge & Murphy, 1984; Kaeppler & Erath, 2016). At the phenotypic level, social competences and shyness are negatively, but not perfectly, correlated, indicating at least partial psychometric independence of the two constructs (Pesenti-Gritti, Scaini, D'ippolito, Fagnani, & Battaglia, 2011). Empirical data indeed shows poorer social competences among socially anxious children with shyness (Spence, Donovan, & Brechman-Toussaint, 1999), and some authors see the pervasive lack of social skills as a pivotal mechanism of SAD (Scaini, Belotti, Ogliari, & Battaglia, 2016; Stravynski, Kyparissis, & Amado, 2010). The inclusion of indices of social competences into the experimental design may thus help better capture the relationships between cortical ERPs to socio-emotional stimuli and individual differences in behaviour and emotionality (Tang, Santesso, Segalowitz, & Schmidt, 2016). Yet, to our knowledge, no study to date has investigated the relationship between social competences and facial processing with ERPs. Moreover, although shyness, social competences, and ERPs evoked by EoEs have all individually been found moderately-to-substantially heritable (Anokhin, Golosheykin, & Heath, 2010; Kagan et al., 1988; Natsuaki et al., 2013; Pesenti-Gritti et al., 2011; Saudino, Carter, Purper-Ouakil, & Gorwood, 2008), no study has to date investigated the nature of their reciprocal relationships.

Here, we sought to address these issues in a twin sample of children from the general population. Firstly, we assessed the association between shyness, social competences and ERPs in response to



different EoEs during a passive viewing task. Secondly, we estimated to what extent genetic and environmental factors influence the interrelationships between ERP responses, shyness, and social competences via multivariate twin analyses.

## **Material and methods**

### ***Participants***

This study is based on the Italian Twin Registry (ITR) (Spatola et al., 2007), a nationwide database of general population twins. Participants belonged to a sample of 130 families of normally-developing twins aged 6–14 who entered the ITR in 2011 in the provinces of Milano and Monza. The majority of children in the sample (>98%) were Caucasian. Participation rate was 77%, leaving 200 twins in 100 complete pairs (mean age:  $9.23 \pm 2.10$  years, 90% aged <12 years) to take part in the study (Bertoletti et al., 2014). None of the participating children carried certified mental/physical handicaps that would require special attention, such as a remedial teacher or differential academic programmes. All procedures had received the approval of our ethical committee, and parents signed an informed consent for all participants.

Zygoty was assigned by the parent-rated Goldsmith questionnaire, which has shown an accuracy of zygoty determination of 94% when matched with DNA samplings (van Beijsterveldt, Verhulst, Molenaar, & Boomsma, 2004). According to the questionnaire, our sample included 38 monozygotic (MZ) (23 female, 15 male) and 62 dizygotic (DZ) pairs, of which 29 were same-sexed (17 male, 12 female) and 33 were of unlike sex.

### ***Protocol: Stimuli, EEG Acquisition and ERP Analysis***

We adopted an ERP protocol employed in previous investigations of the relationships between shyness, ERPs and the development of SAD (Battaglia et al., 2005; Battaglia et al., 2012; Taddei et al., 2012). Six black-and-white standardised pictures of a boy and a girl displaying three EoE (happy, neutral, and angry expressions; time on screen: 1300 ms) were presented under the format of a videogame in an oval aperture that occluded sex-specific features. Participants were instructed to press a response button when a blue circle appeared superimposed around the centre of the picture at 700 ms after face appearance. Therefore, the ERPs relevant to this study were all generated before the motor task, which was only meant to stimulate children's attention and participation. Each stimulus was presented 40 times to ensure sufficient ERP acquisition (total: 120 presentations).

The electroencephalogram (EEG) was continuously recorded from Fz, Cz, Pz, C3, C4, T3, T4 electrodes, left and right mastoids of a 10–20 system with silver–silver chloride electrodes, using a 1000-Hz sampling rate and Oz as recording reference (Neuroscan SynAmp, Neuroscan Labs, USA). Electrodes impedance was kept below 5 k $\Omega$ . The electro-oculogram (EOG) was recorded from electrodes placed vertically above and below the right eye. After the acquisition all channels were re-referenced to the average of the two mastoids. The EEG and EOG were analogically band-pass filtered (0.1–30 Hz) and analysed using Scan 4.4 software (Neuroscan Labs).

EEG data in response to happy, neutral and angry faces were segmented into epochs between -50 and 1300 ms. Epochs were rejected if affected by artefacts (i.e., amplitudes exceeding  $\pm 50$   $\mu$ V). For each subject, a minimum of 20 artefact-free epochs for each facial expression was required for inclusion into the analysis, and an average ERP was separately computed for happy, neutral and angry faces. Our analyses focused on ERP amplitudes rather than latencies, based on similar previous findings by independent groups (Battaglia et al., 2005; Pollak, Cicchetti, Klorman, & Brumaghim, 1997; Tye et al., 2014; Zhang, Li, & Zhou, 2008). ERP amplitudes were measured as the maximum distance of peaks from the baseline within selected latency windows.

While 200 subjects accepted participation, ERP analyses were based on a number of participants

ranging between 185-190, due to removal of participants with insufficient number of artefact-free epochs, or refusals to undergo the ERP protocol on the day of the experiment.

We examined three ERP components evoked by EoE: a negative peak between around 150 ms, identified as a N170, and measured between 50-200 ms; a positive enhancement around 200 ms, identified as a P200, and measured between 100-300 ms; and a late negative component (LNC) around 300-350 ms after stimulus presentation, and measured between 200-400 ms. Analyses focused on data at Cz for N170 and Fz for P200 and LNC, where these ERPs showed the largest activations and topographic distributions, as evident from topographic maps showing maximal activation over Fz electrode for P200 and LNC, and over Cz electrode for N170 (Figure 1 and Figure S1 in Supplementary material), consistently with previous studies (Battaglia et al., 2007; Hum et al., 2013; Sewell, Palermo, Atkinson, & McArthur, 2008; Yuan et al., 2015; Zhang et al., 2008).

[FIGURE 1]

### ***Behavioural Phenotypes***

Data from parent-rated Child Behaviour Checklist (CBCL) (Achenbach & Rescorla, 2001) and Childhood Asperger Syndrome Scale (CAST) (Scott, Baron-Cohen, Bolton, & Brayne, 2002) were available for all participants; data from self-rated Youth Self Report questionnaire (YSR) were also available for participants aged  $\geq 11$  years ( $n=48$ ) (Achenbach & Rescorla, 2001).

As for previous studies of cerebral responses to EoE in children, disposition towards shyness was assessed with a 7 items shyness index (SHY) , ranging from 0 to 35 (Battaglia et al., 2005) originally obtained by principal component analyses (PCA) of items in the Stevenson-Hinde and Glover (1996) (Stevenson-Hinde & Glover, 1996) Shyness to the Unfamiliar, Cloninger's (1994) (Cloninger, Przybeck, Svrakic, & Wetzel, 1994) Harm Avoidance, and the Liebowitz Social Anxiety scales (Battaglia et al., 2004; Liebowitz, 1987).

To build an empirical, concise index of social competences, we included in a PCA the six items of the CBCL Social Competence scale and the seven ‘reverse’ items (items: 1, 5, 10, 15, 21, 27, 35) of the CAST (e.g.: ‘finds it easy to interact with other children’) that assess social skills. This PCA yielded 2 factors with eigenvalue (and percentage of explained variance) of respectively 9.7 (54%) and 1.3 (12%). The following seven items from the first factor had maximal factorial loading (range: 0.75-0.83, reciprocal correlations range:  $r=0.55-0.82$ , all  $p<0.001$ ): 1) joins in playing games with other children easily (CAST), 2) active in organizations/clubs/teams (CBCL), 3) has close friends other than siblings (CBCL), 4) cares to fit in with peer group (CAST), 5) finds it easy to interact with other children (CAST), 6) has good eye contact (CAST), 7) engages in regular weekly social activities (CBCL), and were included into an empirical index of social competences (SOC) ranging from 0 to 16 points. See Supplementary material (Table S1) for psychometric and validity characteristics of SHY and SOC indices.

### ***Statistical Analyses***

#### *Phenotypic Analyses*

The effect of EoEs type (happy, neutral, angry) on each ERP (N170, P200 and LNC) was examined with repeated-measure regression models. The associations between ERPs in response to different EoE and the behavioural variables of SHY and SOC were examined by Pearson correlations.

#### *Twin Analyses*

Multivariate twin designs model the causal sources of covariation between different phenotypes and the partitioning of phenotypic variance and covariance of traits into proportions owing to: (1) additive genetic (A), (2) shared environmental (C), (3) unique environmental (E) factors. The models compare MZ and DZ twins’ phenotypic resemblance assuming correlations of 1.0 for MZ and 0.5 for

DZ pairs between their additive genetic influences, and a correlation of 1.0 for both MZ and DZ pairs for shared environmental influences. Unique environmental influences are uncorrelated for all twin pairs.

Model-fitting analyses on log-transformed scores of SHY, SOC, and ERPs, were performed in OpenMx (Boker et al., 2011) with raw data maximum likelihood estimation incorporating all available data points (thus accounting for missing data). Multivariate models were compared to saturated models and included tests for quantitative sex differences. All analyses controlled for sex and age effects as is standard practise for quantitative genetic model-fitting (McGue & Bouchard, 1984).

We ran an Independent pathway model between SHY, SOC, and ERPs. Unlike the Cholesky decomposition, the Independent pathway model has the advantage of not asserting causal priority of one variable over one other (Loehlin, 1996; Rijdsdijk, 2005), and includes etiological influences that are shared between the variables and etiological influences that are specific to each phenotype.

We then proceeded to simplify the full model into progressively more parsimonious models, by deleting paths carrying the minor contributions to the variance/covariance. Submodels were compared by hierarchical  $\chi^2$  tests (Heath, Neale, Hewitt, Eaves, & Fulker, 1989) and on the basis of the Akaike information criterion ( $AIC = \chi^2 - 2df$ ; (Akaike, 1987)), where the lowest AIC reflects a balance between goodness of fit and parsimony. Comparisons between the full Independent pathway model and two other multivariate models (the Cholesky decomposition model and the Common pathway model) are reported in the Supplementary material (Table S4).

## **Results**

### ***Phenotypic Results***

No differences emerged between N170 ( $t=-0.20$ ,  $p=.84$ ) or P200 ( $t=-.27$ ,  $p=.79$ ) amplitudes in response to the different EoEs. The LNC amplitude showed an effect of EoE type ( $t=-12.96$ ,  $p<.001$ ). Post hoc analyses revealed that LNC amplitude was increased in response to angry faces compared to neutral ( $t=-12.49$ ,  $p<.001$ ) and happy ( $t=-12.90$ ,  $p<.001$ ) faces, while no differences emerged between LNCs to neutral and happy faces ( $t=0.56$ ,  $p=.58$ ).

Pearson correlations showed that SHY and SOC did not significantly correlate with the N170 ( $r$  between  $-.05$  and  $.04$ ), or the P200 ( $r$  between  $-.14$  and  $-.01$ ) in response to happy, neutral, or angry expressions (Table 1). LNC in response to happy and neutral faces showed a significant negative correlation with SHY, and LNC across all three EoEs showed a significant positive correlation with SOC (Table 1). As N170 and P200 did not correlated with SHY or SOC, only LNC amplitude was included in subsequent analyses. The association of SHY and SOC with LNC did not vary substantially depending on the facial expression, and the LNC amplitudes in response to the three different EoEs were highly correlated with one another ( $r$  between  $.63$  and  $.73$ ). Considering this high overlap between LNC across the three EoEs, a composite score (LNC composite, sum of LNC amplitudes to happy, neutral and angry faces) was calculated for each participant to obtain a robust measure of electrophysiological responses to facial expressions and limit the number of measures included in multivariate twin analyses (Table 1).

Consistent with the individual correlations between LNC for anger, happiness, neutrality and the 2 behavioural indices of SHY and SOC, the LNC composite correlated negatively with SHY and positively with SOC, and significantly in both cases (Table 1). A moderate, negative correlation emerged between SHY and SOC, as expected (Pesenti-Gritti et al., 2011).

[TABLE 1]

### ***Multivariate Twin Results***

**Table 2** shows the results of multivariate analyses. Common and specific C influences (submodels 3 and 4), and common E influences (submodel 5) could be dropped without significant fit deterioration, implying that the covariation between LNC, SHY and SOC could be entirely explained by a single, common A factor. The specific A factor for SHY could successively be dropped (submodel 7). Therefore, submodel 7 was retained as the final, best-fitting model (**Figure 2**). The paths from the common A factor to LNC and SOC were positive and significant, whereas the path from the common A factor to SHY was negative, consistent with the signs of the phenotypic correlations. **Table 3** shows the genetic and environmental contributions accounted for by common and specific effects under the best-fitting model. The common genetic factor explained a significant proportion of the genetic variance of the three measures (100% of genetic variance for SHY, 14% for SOC and 13% for LNC).

[TABLE 2]

[FIGURE 2]

[TABLE 3]

## Discussion

We investigated for the first time the association between shyness, social competences and ERP responses to EoEs in a twin sample of general population children. Our data show that both behavioural dimensions were associated with late – but not early – ERPs in response to facial expressions of happiness, neutrality and anger. We further show that the phenotypic covariation between shyness, social competences and electrophysiological responses to socio-emotional stimuli could be entirely explained by common genetic factors, without significant environmental effects.

Previous work has documented a relationship between biased processing of EoEs and childhood shyness both at the behavioural identification (Battaglia et al., 2004) and at the ERP (Battaglia et al., 2005; Hum et al., 2013; Lewis et al., 2007; Thai et al., 2016) levels, sometimes - but not always - with significant differences between amplitudes and type of expression (Battaglia et al., 2005). Our results suggest that emotions modulated the amplitude of the late component (LNC), but not of early components (N170 and P200). By examining the association between ERPs and SHY, we found a negative association between SHY and the amplitude of LNC, but not of earlier components. This result indicates that children with higher shyness show more negative (i.e., increased) amplitude in a frontal ERP component that may reflect impairments in more contextual/cognitive processing of emotional facial stimuli, rather than in basic sensory processes. The association with shyness is consistent with previous studies examining similar fronto-central negative components around 300 ms in relation to childhood shyness and anxiety (Hum et al., 2013; Lamm et al., 2014; Lewis et al., 2007). In addition, we expand on previous work on the electrophysiology of childhood shyness, by showing that this LNC was further positively associated with an index of social competences (SOC). While there is reasonable consensus on identifying psychometric indices for childhood dispositions towards shyness and avoidance of the unfamiliar, the delineation and measurement of effective social functioning and competences in childhood are less well defined (Ordonana et al., 2013). Here, the significant correlation between SOC, LNC and ERPs response to EoEs, however, indicates that social competences should be an additional component to consider when studying brain responses to EoEs. This result points to a coherent association between increased shyness, lower social competences and atypical brain responses to facial expressions.

Furthermore, we investigated the aetiological architecture underlying the association between ERPs, shyness and social competences with twin analyses. In particular, we examined whether - and to what extent - same or different genetic/environmental factors account for the simultaneous covariation between SHY, SOC, and a composite of LNC amplitudes in response to EoEs. Our multivariate



results show that the covariation between SHY, SOC and LNC could be entirely explained by a single factor capturing shared genetic influences between these phenotypes, revealing a coherent etiological structure at the basis of the correlations between shyness, social competences, and cortical ERP responses to other children's facial expressions. Our univariate results (Table S3 in Supplementary material) indicate that SHY, SOC and LNC are substantially heritable, with heritability estimates of .54, .72 and .44, respectively. These results are in line with previous twin studies examining these constructs separately (Anokhin et al., 2010; Eley et al., 2003; Pesenti-Gritti et al., 2011; Shakeshaft & Plomin, 2015). We also report for the first time that a significant proportion of the genetic influences that shape electrophysiological responses to socio-emotional signals (EoE) also regulate childhood shyness and social competences. In keeping with the results of phenotypic analyses, shared additive genetic influences showed opposite effects on the covariation between the LNC and the two divergent behavioural dimensions of shyness and social competences, empirically represented by the SHY and SOC scales. Our results suggest that, insofar as the brain appears to be 'wired for' social communication among individuals (Wilmer et al., 2010), there seems to be a coherent architecture linking the etiological, the neurofunctional, and the behavioural levels in this specific field of socio-emotional functioning. Future studies may aim to extend these investigations to a wider array of information processing stages and cognitive processes, for example by investigating further ERP components such as late positive potential components (Hajcak, MacNamara, & Olvet, 2010; Kujawa, MacNamara, Fitzgerald, Monk, & Phan, 2015), to possibly gain additional mechanistic insight into the nature of emotional information processing in broadly-defined social anxiety.

Two main limitations are in order. First, this is a large sample for an ERP study, but a relatively small one for twin modelling. This implies reduced power to detect shared environmental effects, which could be dropped from our multivariate model. The sample size further prevented us to examine how these results may vary with age. Future larger, better-powered studies could address whether shared

environmental factors may play a role in the covariation between these phenotypes, and whether the contribution of genetic and environmental factors may vary with development. Second, behavioural data were solely derived from questionnaires filled in by mothers, as the duration of the ERP procedures prevented the adoption of lengthy and potentially stressful direct clinical and behavioural assessments. This may have not fully captured the complexity of behavioural phenotypes. However, our psychometric results (Table S1 in Supplementary material) indicate good face validity for both SHY and SOC indexes, and mothers of anxious children have been found to report reliably on their offspring's social competences (Udy, Newall, Broeren, & Hudson, 2014).

Overall, our results converge in indicating a significant, shared heritable basis for childhood shyness, social competences, and general electrophysiological responses to other children's socio-emotional cues. Our ERP results can be compounded with available neuroimaging data, given the premise of a relative imbalance between cortical and limbic activation in response to socio-emotional stimuli in SAD (Miskovic & Schmidt, 2012) and the growing evidence of an association between SAD and altered limbic (especially amygdalar) reactivity to socio-emotional signals in both adolescents (Battaglia et al., 2012; Blair et al., 2011) and adults (Etkin & Wager, 2007). Inasmuch as ERP responses map valid pathogenetic junctures in the transition from childhood shyness to full-blown SAD, these indices could constitute valuable biomarkers for the early identification of risk for SAD before its onset in adolescence, as well as candidate targets in the context of treatment and outcome evaluation. Longitudinal neurophysiological studies on emotional processing of facial expressions are needed to support this growing field of research, and establish the predictive value of ERPs for later psychopathology.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

All procedures had received the approval of our ethical committee, and parents signed an informed consent for all participants.

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## Tables

**Table 1. Phenotypic and Within-Pair Twin Correlations among variables**

			<b>LNC Happy</b>	<b>LNC Neutral</b>	<b>LNC Angry</b>	<b>LNC Composite</b>	<b>SHY</b>	<b>SOC</b>
	<b>Mean</b>	<b>SD</b>	<b>Phenotypic Correlations in the Whole Sample</b>					
<b>LNC Happy</b>	-4.50	5.94	1					
<b>LNC Neutral</b>	-4.63	5.82	0.65**	1				
<b>LNC Angry</b>	-4.91	6.26	0.73**	0.63**	1			
<b>LNC Composite</b>	-14.19	15.83	0.90**	0.86**	0.90**	1		
<b>SHY</b>	11.38	6.35	-0.22**	-0.26**	-0.13	-0.23**	1	

<b>SOC</b>	10.87	2.21	0.26**	0.20**	0.21**	0.25**	-0.30**	1
			<b>Within-Pair Twin Correlations</b>					
<b>MZ</b>			0.65**	0.50**	0.43*	0.65**	0.77**	0.78**
<b>DZ</b>			0.31*	0.32*	0.18	0.40*	0.51**	0.34*

\* $p < 0.05$ ; \*\* $p < 0.01$

DZ, Dizygotic; LNC, amplitude (in  $\mu\text{V}$ ) of a late negative Event-Related Potential measured at Fz in response to facial expressions of happiness ('LNC Happy'), neutrality ('LNC Neutral') and anger ('LNC Angry'), and as a composite of the three expressions ('LNC Composite'); MZ, Monozygotic; SHY, Shyness; SOC, Social Competences.

**Table 2. Multivariate Model-Fitting results encompassing: LNC amplitude at Fz electrode, Shyness and Social Competences**

Model	EP	-2LL	df	AIC	ctm	Diff.LL	Diff.df	p
Model 1. Saturated	54	-2990.99	503	-3996.99	-	-	-	-
Model 2. Full Independent pathway model	21	-2967.52	536	-4039.52	1	23.47	33	0.89
Model 3. Model 2+C <sub>C</sub> =0	18	-2966.91	539	-4044.91	2	0.61	3	0.89
Model 4. Model 3+C <sub>S-LNC</sub> , C <sub>S-SHY</sub> , C <sub>S-SOC</sub> =0	15	-2965.35	542	-4049.35	2	2.17	6	0.90
Model 5. Model 4+E <sub>C</sub> =0	12	-2960.19	545	-4050.19	2	7.33	9	0.60
Model 6. Model 5+A <sub>C</sub> =0	9	-2935.16	548	-4031.16	2	32.36	12	<0.001
<b>Model 7<sup>a</sup>. Model 5+A<sub>S-SHY</sub>=0</b>	<b>11</b>	<b>-2957.19</b>	<b>546</b>	<b>-4049.19</b>	<b>2</b>	<b>10.33</b>	<b>10</b>	<b>0.41</b>
Model 8. Model 7+A <sub>S-LNC</sub> =0	10	-2938.80	547	-4032.80	2	28.72	11	<0.001
Model 9. Model 7+A <sub>S-SOC</sub> =0	10	-2931.69	547	-4025.69	2	35.83	11	<0.001

A, additive genetic factors; AIC, Akaike information criterion; C, shared environmental factors; ctm, compared to model; *df*, degrees of freedom; Diff.*df*, difference in degrees of freedom; Diff.LL, difference in log likelihood statistic; E, unique environmental factors; EP, estimated parameters; LNC, composite score of the amplitudes (in  $\mu\text{V}$ ) of the late negative ERP component in response to happy, neutral and angry expressions; SHY, Shyness; SOC, Social Competences; -2LL, -2 log likelihood statistic.

The subscript C indicates that the influence of the factor is common to the phenotypes, while the subscript S indicates that the influence of the factor is specific, or uncorrelated among phenotypes.

<sup>a</sup> Boldface type indicates the best-fitting model.

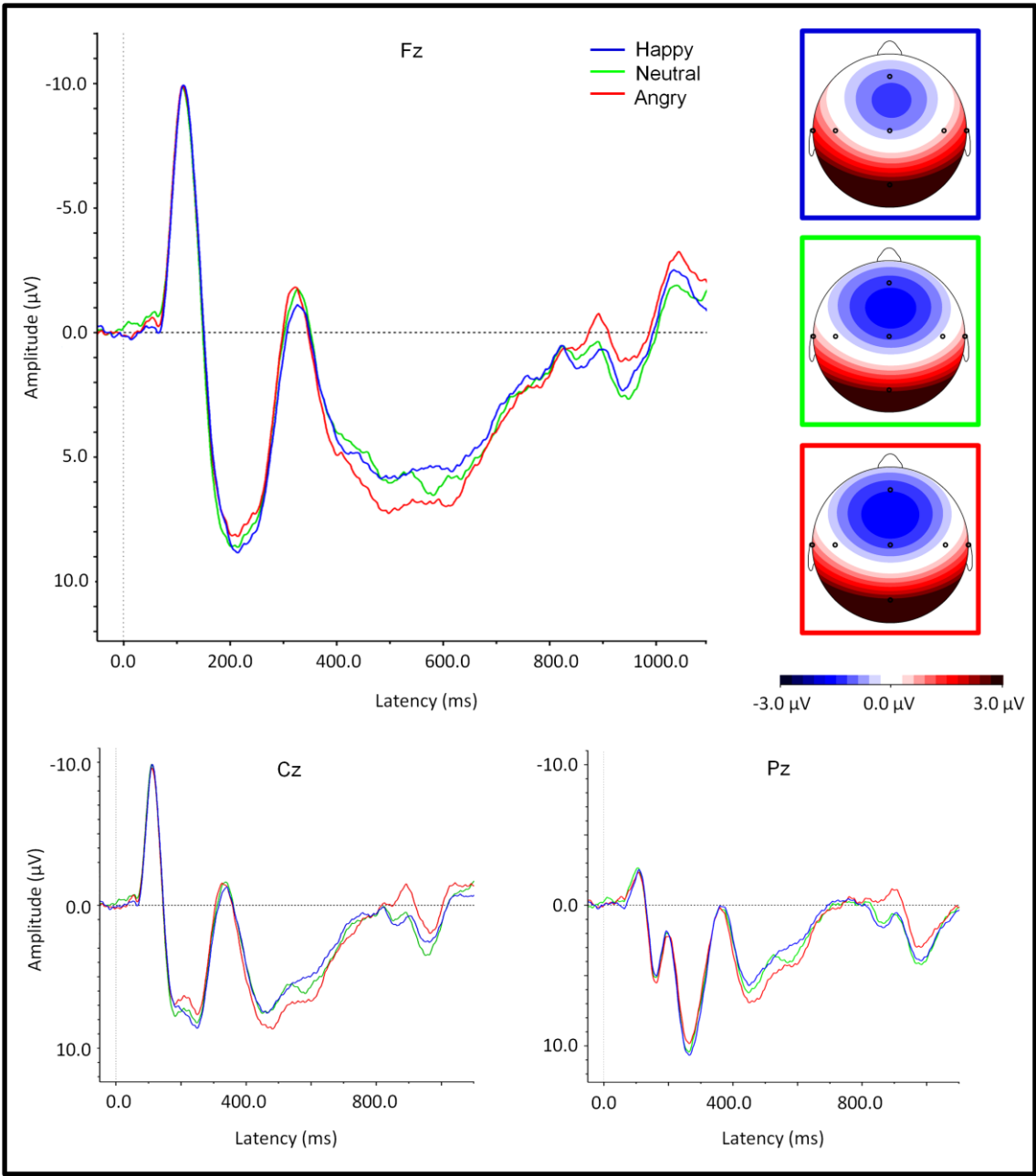
**Table 3. Genetic and environmental contributions accounted for by common and specific etiological factors under the best-fitting Independent pathway model.**

	<b>Genetic and Environmental Contributions</b>								
	<b>V<sub>ac</sub></b>	<b>V<sub>as</sub></b>	<b>V<sub>cc</sub></b>	<b>V<sub>cs</sub></b>	<b>V<sub>ec</sub></b>	<b>V<sub>es</sub></b>	<b>V<sub>a</sub></b>	<b>V<sub>c</sub></b>	<b>V<sub>e</sub></b>
<b>LNC Composite</b>	0.08 (0.01; 0.18)	0.52 (0.31; 0.69)	-	-	-	0.40 (0.26; 0.61)	0.60 (0.39; 0.74)	-	0.40 (0.26; 0.61)
<b>SHY</b>	0.77 (0.63; 0.86)	-	-	-	-	0.23 (0.14; 0.37)	0.77 (0.63; 0.86)	-	0.23 (0.14; 0.37)
<b>SOC</b>	0.10 (0.02; 0.23)	0.63 (0.42; 0.76)	-	-	-	0.27 (0.16; 0.46)	0.73 (0.54; 0.84)	-	0.27 (0.16; 0.46)

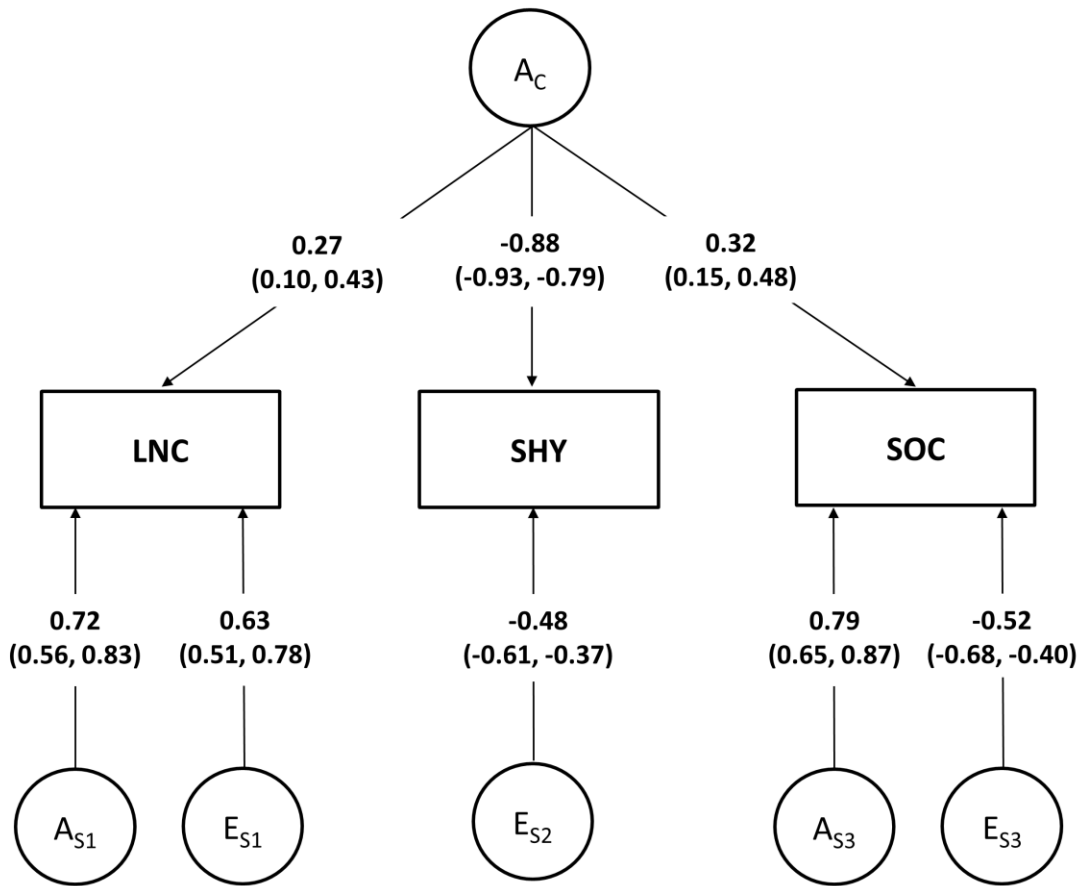
V<sub>ac</sub> variance explained by common additive genetic influence; V<sub>as</sub>, variance explained by specific additive genetic influences; V<sub>cc</sub> variance explained by common shared environmental factors; V<sub>cs</sub>, variance explained by specific shared environmental factors; V<sub>ec</sub> variance explained by common unique environmental factors; V<sub>es</sub>, variance explained by specific unique environmental influences; V<sub>a</sub>, variance explained by additive genetic factors; V<sub>c</sub>, variance explained by shared environmental factors; V<sub>e</sub>, variance explained by unique environmental factors.

Figures

**Figure 1.** Grand averages of ERP responses to happy (blue), neutral (green) and angry (red) expressions at Fz, Cz and Pz electrodes, and topographic maps of LNC.



**Figure 2.** Best-fitting Independent Pathway model of LNC amplitude, Shyness and Social Competences.



$A_C$ , common additive genetic influences;  $A_{S1-S3}$ , specific additive genetic influences;  $E_{S1-S3}$ , specific unique environmental influences; LNC, composite score of the amplitudes (in  $\mu V$ ) of the late negative ERP component in response to happy, neutral and angry expressions; SHY, Shyness; SOC, Social Competences; 95% Confidence Intervals in parentheses.